Table

Patient Ancestry	8/8 URD	7/8 URD	dCB	No 7-8/8 URD/dCB
Europeans N = 605	397/605 (66%)	97/605 (16%)	103/605 (17%)	8/605 (1%)
Non-Europeans N = 279	74/279 (26.5%)	55/279 (20%)	115/279 (41%)	35/279 (12.5%)
African (n = 95)	10/95 (11%)	24/95 (25%)	37/95 (39%)	24/95 (25%)
White Hispanic (n = 59)	16/59 (27%)	17/59 (29%)	19/59 (32%)	7/59 (12%)
Asian (n = 66)	20/66 (30%)	8/66 (12%)	37/66 (56%)	1/66 (1%)

between 10/2005-8/2014. 8 HLA-allele matched URDs were given priority if available; otherwise HLA-mismatched URDs or double-unit CB (dCB) grafts were chosen.

Results: Of 884 patients, 623 (70%) received a 7-8/8 URD transplant, 218 (25%) underwent dCBT & 43 (5%) had no URD/dCB graft. The distribution of 8/8 URD, 7/8 URD, dCB & no URD/dCB grafts is shown (Table). The majority (66%) of Europeans received an 8/8 URD whereas the majority of non-Europeans received either a mismatched URD or dCB graft. 35/43 (81%) of patients without URD/CB grafts had non-European origins, & no URD/dCB grafts were seen in 1% of Europeans versus 12.5% of non-Europeans. When non-Europeans were subdivided into the largest minority groups we found African, White Hispanic & Asian patients were very unlikely to have a matched URD, were most likely to receive dCB grafts, & African ancestry patients were the most likely (one quarter) to have no URD or dCB graft. Interestingly, there was no difference in 8 allele donor recipient HLA-match grade of European (median 5/8, range 2/8-8/8) & non-European (median 5/8, range 1/8-8/8) dCBT recipients. When the origin of dCB grafts was analyzed we found that overall 71% of units for European ancestry patients were domestic as compared to 78% of units for non-Europeans. However, in African & white Hispanic patients 86% & 83% of CB units were obtained from the domestic inventory, respectively.

Conclusion: CB extends transplant access to all patients & is especially important for minorities who are unlikely to have a matched URD. The fact that over 80% of units used in African & white Hispanic patients were domestic, that these patients will be very unlikely to identify a matched URD regardless of the size of the global volunteer donor registry, & that some minority patients do not have suitable CB grafts emphasizes the critical importance of the funding of US public CB banks.

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The Impact of Amino Acid Variability Defines a Functional Distance Predictive of Permissive HLA-DPB1 Mismatches in Hematopoietic Cell Transplantation

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A major challenge in unrelated hematopoietic cell transplantation (HCT) is the prediction of permissive HLA mismatches, i.e. those associated with lower clinical risks compared to their non-permissive counterparts. For HLA-DPB1, a clinically prognostic model has been shown to be matching for T-cell epitope (TCE) groups assigned by cross-reactivity of T-cells alloreactive to HLA-DPB1*09:01, however the molecular basis of this observation is not fully understood. Here we have mutated amino acids (aa) in 10 positions of HLA-DPB1*09:01 to other naturally occurring variants, expressed them by lentiviral vectors in B cell lines and quantitatively measured allorecognition by 17 CD4+ T-cell effectors from 6 unrelated individuals. A significant impact on the median alloresponse was observed for peptide contact positions 9, 11, 35, 55, 69, 76 and 84, but not for positions 8, 56 and 57 pointing away from the groove. A score for the "functional distance" (FD) from HLA-DPB1*09:01 was defined as the sum of the median impact of polymorphic aa in a given HLA-DPB1 allele on T-cell alloreactivity. Established TCE group assignment of 23 alleles correlated with FD scores of $\leq$0.5, 0.6-1.9 and $\geq$2 for TCE groups 1, 2 and 3, respectively. Based on this, prediction of TCE group assignment will be possible for any given HLA-DPB1 allele. *In silico* TCE group classification was performed for currently 328 HLA-DPB1 alleles encoding distinct proteins for which T-cell crossreactivity patterns are unknown, with subsequent functional confirmation for 7/7 of them. These findings have practical implications for the applicability of TCE group matching in unrelated HCT, and provide new insights into the molecular mechanisms underlying this model. The innovative concept of FD opens new potential avenues for risk prediction in unrelated HCT.

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Spousal Hematopoietic Stem Cell Transplantation for Post-Transplant Relapse/Rejection

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Topic Significance & Study Purpose/Background/Rationale: HLA haploidentical stem cell transplantation (SCT) has expanded donor sources from family members. Nevertheless, some patients have no donor candidate and no time to select a suitable donor, especially in post-transplant relapse or rejection. In kidney or liver transplantation, on the other hand, spousal transplant has been routinely performed. In this study, we presented six cases of spousal SCT for post-transplant relapse/rejection, and discussed the possibility of spousal SCT.

Methods, Intervention, & Analysis: Six patients (M/F 4/2, 25-53 years old) underwent SCT from their spouse at Hyogo College of Medicine between October 2008 and November 2013 permission of IRB. Original diseases were acute leukemia (AML 2, ALL 2, MLL 1) and one case of NHL. All patients received a third SCT for post-transplant relapse except for one undergoing SCT for graft rejection after unrelated SCT. HLA disparity in GVH/HVG directions were 2/4, 3/3, 2/2, 5/6, 2/1, and 3/3 antigens in HLA A, B, DR. The conditioning regimen consisted of FLU/MEL/ATG with or without 3 Gy of TBI for relapse cases, and ATG plus 4 Gy of TBI for the rejection case.

GVHD prophylaxis consisted of the continuous infusion of tacrolimus, 1 mg/kg/day of methylprednisolone, and 15 mg/kg/day of MMF. PBSC containing 1.78-8.46 * 10e6/kg of CD34+ cells were transplanted in all cases.

Findings & Interpretation: Granulocyte engraftment was achieved on days 9-11 in all cases. Complete spousal chimerism in PB was confirmed on days 3-13 by STR-PCR. Acute GVHD was controllable except in the rejection case, who died of grade IV GVHD on day 39. All five relapse cases achieved complete remission once, and three could be discharged. One patient died of VOD/SOS on day 62, and one patient was transferred to her local hospital. The remaining four patients excluding GVHD and VOD/SOS cases finally developed disease relapse (in BM 2, CNS 2) on days 106-334, and died as a direct result on days 152-548. Discussion & Implications: Since these cases are refractory and they received their third SCT, we cannot refer to the GVL effect, and GVHD would be acceptable in spousal SCT. The immune recovery remains to be elucidated over a long-term follow-up.

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Pretransplant Sirolimus Improves Outcome of Haploidentical Peripheral Blood Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Patients with Severe Aplastic Anemia

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In a pilot study, we carried out Haploidentical transplantation for 10 patients with severe aplastic anemia (SAA) using peripheral blood stem cell (PBSC) graft and post-transplantation cyclophosphamide (PTCY). The conditioning comprised of Fludarabine 150 mg/m^2, CY 30 mg/kg, horse ATG 45 mg/kg and Melphalan 120 mg/m^2, followed by PTCY 50 mg /kg on D+3, +4 and cyclosporine and mycophenolate from D + 5. Prompt engraftment was followed by early alloreactivity, resulting in transplant-related mortality in 4 of the first 5 patients, all with NK Ligand mismatched donors. In the subsequent 5 patients, Sirolimus was introduced from Day -7 to maintain a trough level of 8-14 ng/ml on the day of transplant and was continued for 12 months post-transplant, with a reduced trough level for cyclosporine. All 5 patients had prompt engraftment with 78-100% donor chimerism and mild chronic GVHD in one patient only. The only significant toxicity observed in these patients was Sirolimus associated acneform lesions. Analysis of Regulatory T cells at 45 days posttransplant was 0.09 $\pm$ 0.13% in the first 3/5 patients compared to 2.6 $\pm$ 0.77% in those receiving Sirolimus (p=0.001). Our study demonstrates that NK cell ligand mismatched donors are associated with early alloreactivity following Haploidentical PBSC transplantation for SAA but addition of Sirolimus to PTCY improves tolerance and outcome.

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The Impact of HLA Mismatch Only in the Host-Versus-Graft Direction on the Outcome of Related Hematopoietic Stem Cell Transplantation for Patients with HLA-Homozygous Haplotypes: A Retrospective Analysis of the JSHCT HLA Working Group Study

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Background: Almost 1% of the Japanese population has HLA-homozygous haplotypes (the same HLA haplotypes). An HLA mismatch between patients with HLA-homozygous haplotypes and their children or parents is absent in the graft-versus-host (GVH) direction. Hematopoietic stem cell transplantation (SCT) from a haploidentical donor with HLA mismatch only in the host-versus-graft (HVG) direction was feasible using standard GVHD prophylaxis (Ikegame K, et al. IJH 2012). However, this should be validated in a larger cohort.

Methods: We analyzed 229 patients with hematologic malignancies who had homozygous HLA-A, -B, and -DR antigens and received their first allogeneic SCT from a related donor without an HLA mismatch in the GVH direction between 1998 and 2012 in Japan. In total, 155 patients received SCT from an HLA-matched related donor (homo-to-homo SCT) and 74 received SCT from a haploidentical donor with HLA mismatch only in the HVG direction (hetero-to-homo SCT). High-risk disease and the use of tacrolimus were more frequently observed in the hetero-to-homo SCT group. The number of HLA mismatches in the HVG direction was 1 in 16 patients, 2 in 27 patients, and 3 in 31 patients. The impact of hetero-to-homo versus homo-to-homo SCT was analyzed after adjusting for transplant year, age, and other significant variables.

Results: There was no significant difference in the cumulative incidence of neutrophil engraftment and severe acute GVHD between the hetero-to-homo and homo-to-homo SCT groups (neutrophil engraftment at 50 days, 91% vs. 95%; adjusted hazard ratio (aHR) 1.05, P = 0.768; severe acute GVHD at 100 days, 10% vs. 5%; aHR 1.68, P = 0.320). Non-relapse mortality was significantly higher in the hetero-to-homo SCT group than in the homo-to-homo SCT group (26% vs. 10% at 5 years; aHR 2.42, P = 0.013), whereas there was no significant difference in the relapse rate. This resulted in non-significant lower overall survival in the hetero-to-homo SCT group (35% vs. 57% at 5 years; aHR 1.41, P = 0.083).

Conclusions: Hetero-to-homo SCT is usually considered only when transplantation should be performed immediately for high-risk disease. Therefore, differences in patient background between the homo-to-homo and hetero-to-homo SCT groups may have biased the comparison. However, it should be noted that there was no significant difference in neutrophil engraftment as well as severe acute GVHD. Although non-relapse mortality and overall mortality rates were higher in the hetero-to-homo SCT group than